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Aortic Graft Infections

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Aortic graft infections are among the most challenging and taxing problems encountered by vascular surgeons. Patients with these infections are often elderly, frail, and severely ill with multiple medical comorbidities; they are poorly equipped to tolerate the extensive, complex operations usually required to treat the problem. Complete resection and excision of all infected graft material and debridement of vascular structures are usually necessary to eradicate infection. Immediate restoration of flow to critical vascular beds by alternate anatomical routes or with in situ replacements that minimize the risk of recurrent infection challenge the skill and ingenuity of the vascular surgeon. Despite a great deal of progress in the treatment of aortic graft infections, morbidity and mortality remain higher than in any other vascular condition (1–3).

I. PATHOGENESIS

Vascular grafts are foreign bodies that can be primarily infected by contamination at the time of placement or secondarily infected after implantation by hematogenous, lymphatic, or contiguous spread. The overall incidence of clinically overt graft infection varies according to anatomical site. Aortic grafts confined to the abdominal or thoracic cavity rarely become infected; the incidence ranges from 0.5 to 2% (2). The incidence is higher, from 2 to 6%, when distal anastomotic sites are at the femoral level (4).

Several features of the femoral area predispose to infectious complications. The groin is difficult to clean and incisions placed in the groin are prone to infection and healing problems. Groin incisions that extend obliquely across the inguinal crease tend to gape, and in obese patients they lie buried in moist skin folds. Furthermore, superficial inguinal lymph nodes are usually transected during exposure of the common femoral artery; if they are not ligated, they will bathe a vascular graft in lymphatic fluid that may contain bacteria. Potential sources of graft contamination in this circumstance include open, infected ischemic ulcers of a lower extremity, gangrenous toes, and wounds in any other area drained by the inguinal lymphatics, such as the perineum and perianal area. Another

factor implicating the groin wound in the etiology of vascular graft infections is transient local ischemia during placement of the graft, which may render the wound more susceptible to infection.

The majority of vascular graft infections are initiated at the time of operation (2,3,5). Although direct proof of this is difficult to obtain, the prevalence of *Staphylococcus epidermidis* among offending organisms suggests that skin contamination with the patient's own flora is an important mechanism (6,7). *S. epidermidis* can often be cultured from the gloves of the surgical team, and grafts may be contaminated by this source during placement (8). The presence of *S. aureus* and other nosocomially acquired bacteria is also common and points to other environmental sources of contamination. These include intestinal flora when the gastrointestinal tract is entered or when operations such as cholecystectomy are performed at the time of vascular reconstruction. Laminated thrombus lining the walls of aneurysms has been implicated as a source of contamination and, when cultured, yields bacteria in about 10% of specimens (9,10). *S. epidermidis* is the most common isolate. Postoperative sources of aortic graft infection include wound complications, urinary tract infections, and invasive line sepsis. Early and late hematogenous seeding of grafts can occur during transient bacteremia associated with remote infections or dental procedures (11).

Although bacteria cause most aortic graft infections, other, less common microorganisms such as fungi, mycoplasmas, and mycobacteria have been encountered. *S. epidermidis* is the most common pathogen reported in modern series and outnumbers *S. aureus* infections two to one. Gram-negative and polymicrobial infections are increasingly being encountered but remain less prevalent than gram-positive infections. In many instances, negative cultures are reported despite convincing local evidence of infection, including nonincorporated graft material surrounded by grossly purulent fluid (12). These cases are most likely caused by *S. epidermidis* or other low-virulence organisms that are exposed to perioperative antibiotics at the time of sampling and require fastidious microbiological techniques for growth. Sonication of graft material, growth in tryptic soy broth, and prolonged incubation for several days have been reported to increase the yield of cultures positive for *S. epidermidis* (13).

Methicillin-resistant *S. aureus* (MRSA) has emerged as a serious and prevalent pathogen in some recent series tracking the epidemiology of vascular infections (14). These microorganisms can infect native arteries, destroy vascular tissue, and be difficult to eradicate (15). MRSA appear to be particularly virulent, leading to poor outcomes. In one recent series of 55 MRSA graft infections, 55% of patients died or underwent amputation (14).

The presence of a foreign body, such as an implanted device, increases the risk of infection. Early investigations documented that it takes only 10^2 *S. aureus* organisms to cause an abscess at the site of a suture but 10^6 organisms to cause an infection in normal skin. The vulnerability of foreign materials to infection involves physicochemical properties of the material, impairment of host defenses, and special properties of the bacteria themselves that facilitate their growth in the presence of a biomaterial (16). The biological reaction to an implanted vascular graft comprises an acute inflammatory response in the early stages that progresses to formation of a fibrous capsule or tissue ingrowth. Neutrophils rapidly become associated with any implanted biomaterial in vivo, become prematurely activated by contact with the material, and rapidly lose the capacity to become activated in response to subsequent stimuli, such as the presence of bacteria. Neutrophils in contact with biomaterials rapidly lose their ability to produce superoxide and other re-

active oxygen species and become relatively impotent in their microbicidal activity (17,18). Thus the biomaterial acts as a massive "decoy" that prevents the neutrophils from responding normally to bacteria in the microenvironment. In addition, neutrophil products released in these circumstances may promote dysfunction of new neutrophils entering the microenvironment (19).

Vascular graft materials may vary in their susceptibility to infection by different micro-organisms. Highly textured or rough-surfaced biomaterials, such as textiles made of Dacron (woven or knitted), are more prone to bacterial adherence than smooth-surfaced biomaterials, such as expanded polytetrafluoroethylene (ePTFE) or polyurethane (20). In vivo, the adherence of platelets, plasma proteins, and other blood constituents and varying conditions of shear may dramatically alter the responses of different biomaterials to micro-organisms, and all biomaterials remain susceptible to infection (21,22).

The principal organism responsible for infections of all implanted medical devices, including vascular grafts, is *S. epidermidis*. This organism is a ubiquitous skin commensal with of relatively slow growth and low virulence. It causes chronic infections with local manifestations and little or no systemic toxicity. Pivotal in the pathogenesis of *Staphylococcus epidermidis* infection is the production of multilayered biofilms composed of exopolysaccharides, usually referred to as "slime." The elaboration of biofilms takes place following the adherence of *S. epidermidis* to biomaterials and usually occurs when organisms adhere to one another in microcolonies (23). Adherence of organisms to both polymer surfaces and each other (cell–cell adhesion) is mediated by capsular polysaccharide adhesins (23,24). Mutant bacteria that do not produce adhesins lack cell–cell adhesions and do not produce biofilms (25). Once elaborated, biofilms form a protective shield that allows continued bacterial growth in relatively hostile environments. Bacterial nutrients and metabolic wastes freely traverse the polysaccharide biofilm, but antibiotics do not. Biofilms also alter inflammatory changes, impair host defenses, and promote tenacious adherence of microbial colonies to the biomaterial (26). *S. epidermidis* infections tend to be persistent and refractory to antibiotics; therefore the implant must be removed to clear the infection.

Once established, bacterial infection spreads throughout a vascular graft and eventually involves anastomotic sites. The eventual destruction of vascular tissue leads to the formation of an anastomotic false aneurysm. The first manifestation of a vascular graft infection is often an anastomotic false aneurysm or its most frequent complication, graft thrombosis. When the false aneurysm involves the aortic anastomosis, rupture into the duodenum may occur and produce an aortoduodenal fistula with catastrophic hemorrhage. Although all micro-organisms producing vascular graft infections are associated with false aneurysms, they vary in their propensity to destroy vascular tissue. Gram-negative organisms—such as *Pseudomonas aeruginosa*, *Proteus* species, and *Escherichia coli*—are particularly notorious for their ability to digest vascular tissue (27). These organisms elaborate elastase and alkaline protease, which break down elastin, collagen, fibronectin, and fibrin. In addition to causing vascular disruption and the formation of false aneurysms, many bacteria produce substances that are highly thrombogenic and can induce thrombosis that may be the first manifestation of a vascular graft infection.

Aortic stent grafts would appear to be uniquely predisposed to infection. Tissue ingrowth from surrounding tissues is generally absent (28), and lack of tissue incorporation into prosthetic interstices is widely acknowledged to be a permissive condition for prosthetic infections. In addition, stent grafts are usually surrounded by luminal thrombus, which

may harbor micro-organisms. Despite these theoretical considerations, acute aortic stent graft infections have been reported infrequently. Environmental sources of infection from gloved hands and the operating field are reduced because most commercial stent grafts are jacketed in sterile packages until deployed. In cases of acute stent graft infection, bacteremia was clearly documented (29). Infection may emerge as a significant problem on longer follow-up. In one series with a mean follow-up of 49 months, the incidence of infection of stent grafts requiring removal was an alarming 3.3% (30).

II. CLINICAL PRESENTATION

The clinical presentation of aortic graft infections can be protean and subtle, making the diagnosis difficult. The tempo and severity of the clinical manifestations often depend on the micro-organism. A patient whose infection is caused by a virulent organism—such as *S. aureus*, *P. aeruginosa*, and *E. coli*—presents with systemic signs of sepsis. As an example, a patient with a vascular graft who has persistent fever, chills, and an elevated white blood cell count with a left shift should be suspected of having a vascular graft infection. Virulent micro-organisms also tend to cause earlier manifestations of infection, with the interval between implantation of the graft and diagnosis of infection being months. Very early graft infections, diagnosed within weeks of implantation, are often associated with wound complications that involve vascular grafts by contiguous spread.

In contrast, patients with graft infection caused by a low-virulence organism, such as *S. epidermidis*, present later, often years after placement (7). Systemic signs and symptoms are usually mild or absent. These patients most often present with local manifestations, such as a chronic groin sinus that discharges small amounts of purulent material, a chronic wound infection with exposed graft, femoral anastomotic false aneurysm, or aortofemoral bypass limb thrombosis. They may have low-grade fever and mild constitutional symptoms, but overt signs of sepsis are absent. The white blood cell count is usually normal or only mildly elevated, but the erythrocyte sedimentation rate is often elevated. A patient presenting with a femoral anastomotic false aneurysm or limb thrombosis who has an elevated erythrocyte sedimentation rate should be suspected of having a graft infection.

Patients presenting with massive gastrointestinal hemorrhage from an aortoduodenal or aortoenteric fistula have frequently had lesser episodes of bleeding hours to days before the major episode. These are often referred to as "herald" or "sentinel" episodes of bleeding and offer a window of opportunity for the diagnosis and management prior to the onset of exsanguinating hemorrhage. Any patient with an aortic graft who has an episode of upper or lower gastrointestinal bleeding should be suspected of having an underlying aortoenteric fistula, and an expeditious workup is important. Chronic gastrointestinal bleeding can also occur in patients with an aortoenteric fistula but is more often associated with an enteric erosion. This condition, often referred to as a "graft–enteric erosion," differs from aortoenteric fistula in that the body or limb of the aortic graft erodes into bowel and the aortic suture line is not involved. This produces chronic bleeding from the eroded bowel mucosa, analogous to bleeding from an ulcer, and patients may present with chronic anemia. The diagnosis should be suspected in a patient with an aortic graft who has anemia, stool positive for occult blood, and fever.

Hydroureteronephrosis may also be the first manifestation of an aortic graft infection. This can develop if the ureter becomes obstructed as a result of perigraft inflammation and may be bilateral or unilateral, depending on the extent of infection.

III. DIAGNOSIS

Because the manifestations of aortic graft infections are so varied and subtle and the consequences of a missed diagnosis may be lethal, imaging tests are important (31). The types of imaging and other diagnostic tests used are based on the clinical presentation. Computed tomography (CT) has been the mainstay of diagnostic imaging for a suspected aortic graft infection. CT findings suggestive of infection include ectopic gas, periprosthetic fluid, loss of tissue planes, perigraft inflammatory changes, thickening of adjacent bowel, hydroureteronephrosis, and anastomotic false aneurysm (32). These findings are most specific and useful for late infections. During the immediate perioperative period following implantation, perigraft fluid, air, and inflammatory changes may persist for 2–3 months. After 3 months, postoperative hematoma and gas should resolve and tissue planes return to normal (33).

Magnetic resonance imaging (MRI) has provided an alternative to CT for cross-sectional imaging. In addition to demonstrating the same features seen on CT (periprosthetic air, fluid, and structural abnormalities), MRI is particularly helpful in assessing periprosthetic inflammatory changes. These changes are high intensity signals on T2-weighted images in the tissues surrounding the prosthesis and accurately portray tissue edema (34). Such images can be particularly helpful in assessing the extent of infection, which may determine the operative approach. For example, in a patient with an infection localized to a single distal limb of an aortobifemoral bypass, removal of the entire prosthesis may not be required for adequate treatment of the infection.

Radionuclide scanning has also been used in the diagnosis of vascular prosthetic infections. Scintigraphy with the use of autologous white blood cells labeled with indium 111 (^{111}I) is the most common technique currently used, although the use of white cells labeled with gallium 67, technetium, and other isotopes has been reported (35,36). In addition, scintigraphy based on labeled human immunoglobulin G has been used and may be more sensitive than scintigraphy with white cells (37). A problem with all scintigraphic methods in diagnosing vascular graft infections is the lack of specificity caused by uptake in other organs or tissues that may be contiguous. In addition, faint or no uptake in the presence of limited or low-virulence infection can result in false-negative results. Scintigraphy is most helpful when occult prosthetic infection is suspected. An example would be a patient with an aortic graft presenting with a fever of unknown origin or a complex of other nonspecific symptoms in whom white blood cell scintigraphy identifies the graft as the source.

Arteriography is of limited usefulness in the diagnosis of vascular graft infection but it may, on occasion, demonstrate an aortic false aneurysm or even leakage of contrast into the bowel lumen, which is pathognomonic for an aortoenteric fistula. Arteriography is helpful in planning reconstruction after removal of the prosthesis and is most useful in late infection, when the vascular anatomy may have been altered by progressive occlusive disease. CT angiography may replace conventional angiography and provide additional information obtained by conventional cross-sectional CT imaging.

In patients presenting with gastrointestinal bleeding and suspected aortoenteric fistula, complete upper gastrointestinal endoscopy with visualization of the third and fourth portions of the duodenum, the most common sites of fistula, is necessary. Even if this study is incomplete, with inability to visualize the distal duodenum or the finding of gastrointestinal lesions such as chronic peptic ulcer that are not actively bleeding, an aortoenteric fistula may still be present. Continued unexplained bleeding mandates operative

exploration to rule out aortoenteric fistula. At the time of operation, the duodenum, proximal jejunum, and any other bowel in contact with an aortic graft must be dissected free to make or exclude this diagnosis.

IV. PREVENTION OF AORTIC GRAFT INFECTIONS

The benefit of short-term antibiotic prophylaxis in preventing wound infections after vascular surgery has been demonstrated in randomized trials (38–40). Most often, a first-generation cephalosporin is administered intravenously shortly before operation, during operation if blood loss is extensive or the operation is prolonged, and 2 h after operation. Some evidence suggests that a more prolonged course for up to 4–5 days after operation or until all invasive lines are removed may provide additional protection (41). In circumstances where patients have infected lower extremity ischemic lesions, culture-specific antibiotics should be administered perioperatively. Also, the use of more specific prophylactic antibiotic therapy should be considered in hospital settings where certain organisms are prevalent, especially when exposure is increased by prolonged preoperative hospitalization.

Attention to intraoperative factors is also important in preventing aortic graft infections. Reoperations and emergency operations are especially prone to wound infections and present additional risks. Meticulous attention to hemostasis and avoidance of wound hematomas and seromas that can become secondarily infected are important surgical goals that are often difficult to achieve in patients anticoagulated during the operation who are also being treated with antiplatelet agents. If possible, these agents should be discontinued one week prior to operation. Ligation and control of femoral lymphatics are also important technical features in preventing aortic graft infections. Electrocautery of lymphatic tissue leads to coagulation necrosis of lymphatic vessels but does not prevent extravasation of lymph fluid. Fibrin glue applied to groin wounds has been shown to decrease lymph drainage and groin would complications (42).

Patients undergoing aortic operations are prone to intraoperative hypothermia; this condition has been shown to impair neutrophil function and increase the incidence of postoperative wound infection (43). Maintenance of normal body temperature should be the goal during major vascular operations. Additional procedures on the gastrointestinal or biliary tract that may result in intraoperative contamination of an aortic graft should be avoided unless the additional procedure is deemed necessary to avoid life-threatening postoperative complications. Hematogenous seeding of a vascular graft is a continuing risk for as long as the graft is in place. Dental work, procedures on the gastrointestinal and genitourinary tracts, and angiographic procedures should be carried out under the protection of prophylactic antibiotics.

V. TREATMENT

The primary goals of treatment are to save life and limb, and these are best accomplished by eradicating infection and maintaining adequate circulation to portions of the body perfused by the infected aortic graft. Secondary goals include minimizing morbidity, restorating of normal function, and maintaining of long-term function without the need for reintervention and risk of amputation.

These goals are best achieved by the removal of all infected graft material and vascular tissues combined with appropriate arterial reconstruction. The currently favored methods